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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KAUSHAL, SUMESH

ART UNIT PAPER NUMBER

1636

DATE MAILED: 09/19/2002

Handwritten signature

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/255,963

Applicant(s)

MA, PETER X.

Examiner

S. Kaushal

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 July 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20,22,23,25-38 and 40-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-20,22,23,25-38 and 40-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Applicant's response filed on 01/01/01 has been acknowledged.

Claims 48-51 were newly filed.

Claim 24 was canceled.

Claims 23, 25-26, 29, 31 34-35, 40 and 47 were amended.

Claims 1-20, 22-23, 25-38 and 40-51 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

► *If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (<http://www.uspto.gov>) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.*

Claim Rejections - 35 USC § 112

Claims 1-20, 22-23, 25-38 and 40-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons of record as set forth in the office action mailed on 03/01/02.

Claims 1, 11, 23 and 34 are indefinite because it is unclear whether the medium into which the hydrogel system is introduced is different from the medium or mixture into which the three-dimensional hydrogel cross-linking was performed.

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The applicant fails to address this rejection in the response filed on 07/01/02 (see page 4). However, applicant admits that the "Applicant's hydrogels are not formed in calcium solutions" (see page 11, para.5, lines 12-15). Therefore it is unclear whether the medium into which the hydrogel system is introduced is different from the medium or mixture into which the three-dimensional hydrogel cross-linking was performed.

Claim Rejections - 35 USC § 103

Claims 1-20, 22-23, 25-38 and 40-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (Carb. Poly. 14:159-178, 1991), Martisen et al (Biotech. Bioeng. 33:79-89, 1989) and further in view of Hauselmann et al (US Patent 5,658,343) and Cao et al (Book of abstracts, BIOT-212, 211thACS National Meeting, New Orleans 1996) for the same reasons of record as set forth in the office action mailed on 03/01/02.

The applicant argues that none of the reference cited teach or suggest selective size control of a three-dimensional hydrogel system by varying cation concentration. Draget does not teach transferring a hydrogel into a medium and '343 patent controls the hydrogel system by mechanical means (response, page 11, para.4). The applicant argues that Martinsen teaches making of alginate beads in aqueous solution of CaCl_2 , wherein the applicants hydrogels is not formed in a calcium solution (response, page 11, para.5). The applicant argues that Martinsen does not describe selective control of the size of a hydrogel whereas applicant can selectively cause inventive hydrogel to swell, shrink or maintain by varying a calcium ion concentration (response, page 12, para.1-2). The applicant argues that considering the publication date of Martinsen (1989) one would believe that Martinsen did not teach what office has been asserting. In addition, the applicant argues that office is using hindsight to assume that Martinsen was teaching volume control of a cross-linked hydrogel (response, page 13, para.1).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the

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time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The applicant fails to consider the combined teaching of the reference cited herein in entirety. The combination and modification of the teachings of the prior art clearly suggested the claimed invention. The arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In this case Draget et al teaches the formation of a gel consisting of mixing 15mM CaCO_3 with sodium alginate solution, then adding 30mM GDL, resulting in a final gel of pH 7 (see, e.g., pg 161, para. 2) only to avoid formation of acidic gels (page 163, para.3). Draget et al also teach that the sodium alginate can be substituted with alginate derived from *Marocystis pyrifera* or *Laminaria hyperbores*, thus altering the viscosity of the gel (pg 161, Table 1; pg 173); and that the dimensions of the gel (e.g. thickness and diameter) are largely a function of the dimensions of the mold into which they form, and can thus be easily modified by one of ordinary skill in the art. Furthermore, maximum gel strength was reached when Ca^{2+} concentration was equivalent to the amount of guluronic acid residues and syneresis become prominent when the calcium contents exceeded this value (page 175, fig-13, page 177 para.3). Thus Draget clearly teaches that variation in calcium ion concentration results in the formation of hydrogels with distinct characteristics.

Martisen teaches that physical properties of beads strongly are dependent upon the composition sequential structure and molecular size of the polymers. The cited art teaches that

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beads with the highest mechanical strength, lowest shrinkage, best stability towards mono-valent cations and highest porosity were made from alginate with contents of L-guluronic acid higher than 70% and average length of G-blocks higher than 15 (page 79, abstract). In addition, the cited art teaches evaluation of stability of Ca-alginate gel beads towards Na⁺ ions by transferring gels beads to solutions containing different concentrations of CaCl₂ (0.001M-0.05M) and measuring the bead volume (shrinkage) every 24 hours for 3 days (page 81 col.1 para.1). The cited art teaches that gel strength and shrinkage is the function of CaCl₂ concentration and gelling time (page 84, col.1-2, fig-7 and 8). In addition the cited art teaches that high gel strength, low shrinkage, high stability towards Na⁺ ions and high permeability are the most advantageous factors for the immobilization of living cells (page 89, col.2).

The applicant's argument that Martinsen does not suggest the invention as claimed is moot, since the invention as claimed fails distinguish that the medium into which the hydrogel system is introduced is different from the medium or mixture into which the three-dimensional hydrogel cross-linking was performed. Therefore, given the broadest reasonable interpretation to the invention as claimed, Martisen clearly suggests selective size control of a three-dimensional hydrogel system by varying calcium ion concentration into which the hydrogel is introduced.

Hauselmann et al teach the method of producing an alginate gel in vitro comprising cells that produce an extracellular matrix, for implantation in vivo (e.g., col. 1, lines 39-60). Hauselmann et al also teach that the molar ratio of calcium ions to carboxyl groups in the gel determines the amount of cross-linking of the gel, as well as the amount of swelling and thus size of the gel (e.g, col 7, lines 29-46, & Figure 6a,b).

Cao et al teach the method of making and using biodegradable calcium alginate gels with osteoblasts in vitro for implantation in vivo to generate bone growth. The osteoblasts were suspended 1% sodium alginate, then 0.2g of CaSO₄ was added to each ml of the admixt to initiate gel formation. The mixture was injected in nude mice, which results in the new bone formation in the transplanted animals (see abstract)

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Draget and Martisen by introducing cells (osteoblasts) as taught by Hauselmann and Cao to the Ca-alginate hydrogels composition. One would have been motivated to do this to utilize the gel as a scaffold for cell growth and differentiation for tissue engineering.

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It would have been further obvious in view Martisen to control the hydrogel shrinkage or swelling by transferring the hydrogels into the solutions that contain different concentration of calcium ions. One would also have been motivated to alter the calcium ion concentration and the ratio of calcium ions to alginate carboxyl groups in order to controlling the amount of gel swelling and shrinkage. One would have been motivate to control hydrogel shrinkage and swelling because these characteristics are highly desirable in tissues engineering for different applications. Therefore, the invention pertaining to specific ion concentrations and the molar ratios that results in hydrogel swelling and shrinking are the result effective variables, which could have been readily determined by one of ordinary skill in the art especially in view of Draget and Martisen. Thus the invention as claimed is prima facie obvious in view of cited art of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If

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attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal

Patent examiner

Scott D. Pribe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER